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RAPID COMMUNICATION

Cocaethylene Is More Potent Than Cocaine in Mediating Lethality

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HEARN, W. L., S. ROSE, J. WAGNER, A. CIARLEGLIO AND D. C. MASH. *Cocaethylene is more potent than cocaine in mediating lethality.* PHARMACOL BIOCHEM BEHAV **39**(2) 531–533, 1991.—Cocaethylene is a pharmacologically active cocaine metabolite that is formed in the presence of ethanol by the activity of liver enzymes. The pharmacology of cocaethylene has not been extensively investigated and its acute toxicity is unknown. The acute toxicity of cocaethylene was compared to cocaine in Swiss-Webster mice. The LD_{50} of cocaethylene was 60.7 mg/kg and 63.8 mg/kg in female and male mice, respectively. In comparison, the LD_{50} of cocaine was 93.0 mg/kg in both female and male mice. These studies demonstrate that the cocaine-alcohol metabolite, cocathylene, is more potent in mediating lethality than the parent drug.

Cocaethylene Toxicity LD_{50} Mice Cocaine Alcohol

COCAETHYLENE (ethylbenzoylecgonine) is a unique cocaine metabolite that is produced in the presence of ethanol by the activity of liver enzymes (5). Significant levels of cocaethylene have been measured in postmortem blood and brain samples from cocaine-related deaths (5). Blood levels ranged in this study from 0.03 to 0.31 mg/l. The highest cocaethylene concentration measured in antemortem blood samples taken from emergency department admissions was 2.3 mg/l (8). Blood concentrations of cocaine associated with behavioral and toxic effects are in excess of 0.1 mg/l. Cocaine levels in blood over 2 mg/l are usually associated with fatalities (12).

The toxic effects of cocaine are produced through complex mechanisms, which include central and peripheral sites of action. Although the mechanisms involved in the lethal effects of cocaine are not well defined, central nervous system effects and direct cardiotoxicity may contribute to cocaine lethality. Several studies have emphasized the variability and unpredictability in the range of fatal doses of cocaine (12,13). Morbidity and mortality are known to be exacerbated by concurrent cocaine and alcohol abuse (6). One possible explanation for these observations is the added effects of cocaethylene in subjects that had combined cocaine with alcohol prior to death. In this study, we report the comparative lethality of cocaine and cocaethylene in mice. The results demonstrate that the cocaine and alcohol metabolite—cocaethylene—is more potent than the parent drug in mediating lethality.

METHOD

Cocaethylene was synthesized from benzoylecgonine by a modification of the method of DeJong (4). In brief, ethanol was substituted for methanol in the synthesis to yield ethylbenzoylecgonine (cocaethylene). The identity and purity of the product were established by melting point determinations, gas chromatography and gas chromatography-mass spectrometry, in comparison with an authentic cocaethylene standard obtained from the United States Drug Enforcement Administration. The optical activity and configuration of cocaethylene were measured by optical rotation and nuclear magnetic resonance spectrometry, respectively. Benzoylecgonine was provided by NIDA, or prepared from cocaine by published procedures (2,4). Cocaine hydrochloride was obtained from Sigma Chemical Company. For lethality studies, cocaethylene base was dissolved in a stoichiometric quantity of 1 N hydrochloric acid and diluted with deionized water to yield a 10 mg/ml stock solution.

Male and female CD-1 outbred Swiss Webster mice (5 to 6 weeks of age) were used in these studies. Mice were housed five per cage under controlled environmental conditions (24°C, 12 h light/dark cycle). Animals were fed a commercially prepared pelleted diet (Purina) and fasted for 12 hours prior to drug administration. Water was provided ad lib. Cocaethylene and cocaine were administered by intraperitoneal injection. Injection volume was standardized at 25 ml/kg. Ten mice were used at

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each dose level. After injection, the mice were placed in home cages and observed for symptoms of toxicity and lethality. Subjects were observed for survival at the following times after drug administration: 10, 20, and 30 min, 1, 2, 3, 6 and 24 hours. No deaths were observed in animals after 30 min. Therefore, lethality was scored 30 min after IP injection of the drugs. Dose-effect functions and the relative potency estimates were calculated using methods described previously for evaluation of quantal dose-effect relationships (3,7). Dose-effect functions were considered significantly different when the 95% confidence limits for their potency ratios did not include 1.00.

RESULTS

Mice treated with cocaine displayed stereotypical behavior and increased motor activity followed by seizures. The behavior of the mice receiving cocaethylene contrasted with the animals receiving cocaine. Cocaethylene-treated mice demonstrated arching of backs and pilorerection, with brief tonic-clonic convulsions.

Dose-lethality curves are shown in Fig. 1. The calculated LD_{50} for cocaine was 92.4 mg/kg in females (95% C.I. 91.4–93.5) and 93.0 mg/kg in males (95% C.I. 91.9–94.1). These values compare favorably with the previously reported LD_{50} determinations in Swiss Webster mice (1). The LD_{50} for cocaethylene was 60.7 mg/kg in females (95% C.I. 59.7–61.8) and 63.8 mg/kg in males (95% C.I. 62.8–64.8). The difference in the dose-effect functions for cocaine and cocaethylene were significant in male and female mice with a relative potency ratio of 1.5. These results demonstrate that cocaethylene is more potent than cocaine in mediating lethality. No significant differences in the toxicity of cocaine or cocaethylene were observed between male and female mice. Using the calculated LD_{50} values, male mice (N = 10) were coadministered ½ of this dose or 46.2 mg/kg cocaine and 30.3 mg/kg cocaethylene. This drug regimen resulted in the predicted 50% lethality, indicating an additive toxicity of cocaine and cocaethylene.

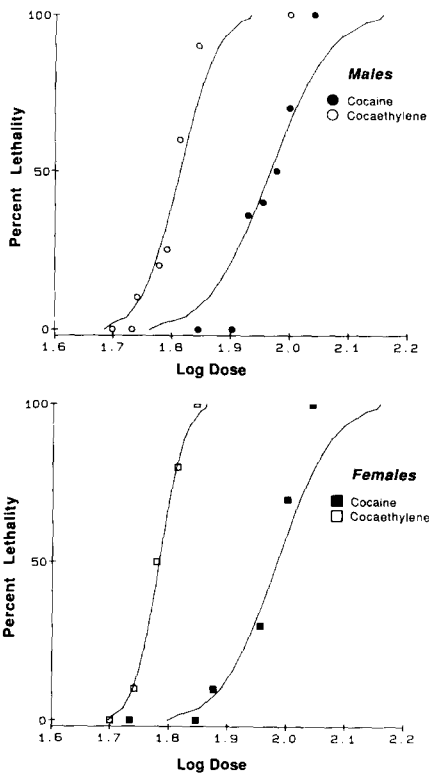

FIG. 1. Lethal effects of cocaethylene (open symbols) and cocaine (closed symbols) in mice. Data represent effects in groups of 10 mice each. LD_{50} values are given in the text.

DISCUSSION

The present study demonstrates that cocaethylene is more potent than cocaine in mediating lethality in mice. The LD_{50} determinations for cocaine were the same in female and male mice and are in agreement with previously published values (1). Lethality studies in animals are difficult to extrapolate to humans. However, medical examiner evaluations of cocaine-related sudden deaths indicate a wide range of cocaine levels that are associated with fatalites. Wetli and Wright reported on 24 deaths from cocaine with quantitative measurements of postmortem blood-cocaine levels (13). The toxicological results indicate that many fatalities are associated with relatively low blood-cocaine levels (<0.5 mg/l).

One possible explanation for these low dose cocaine fatalities is the additive effects of cocaethylene in subjects that had used cocaine and alcohol prior to death. The Drug Abuse Warning Network (DAWN) has identified alcohol in combination with cocaine as the most common substance use pattern found among individuals presenting to emergency rooms with substance abuse problems in twenty-four metropolitan areas (10). Simultaneous cocaine and alcohol use was the second most prominent two-way drug combination reported for substance abuse-related deaths in the DAWN system. Morbidity and mortality are exacerbated by concurrent use of cocaine and alcohol (6). Risk factor analysis is needed to determine the precise contribution of cocaethylene to the epidemic of cocaine-related sudden deaths occuring in many metropolitan areas. However, the results of the present study suggest that the combination of cocaine and alcohol may result in a potentially lethal mix due to the additive toxicity of cocaethylene.

The lethal effects of cocaine are produced through complex mechanisms, which include both central and peripheral sites of action. We have previously demonstrated that cocaethylene displays high affinity for the dopamine transporter (5). Studies of the lethal effects of cocaine in rats indicate that the D_1 dopamine antagonist, SCH 23390 protects against cocaine-induced death, while the D_2 antagonist, haloperidol, was not effective in blocking cocaine lethality (15). The cardiovascular actions of cocaine are known to be potentiated by atropine (14). In keeping with the structural similarity to atropine, both cocaine and cocaethylene are competitive antagonists of muscarinic receptors (9,11). It has been suggested that in humans, the additive effects of muscarinic blockade and sympathetic stimulation by cocaine administration may lead to serious toxicity (16). The contribution of central and peripheral mechanisms to the combined toxicity of cocaine and cocaethylene warrants further study.

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